

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

**0 361 680
A2**

12

EUROPEAN PATENT APPLICATION

21 Application number: 89308659.5

61 Int. Cl.⁵: **A61K 9/46 , A61K 31/485 ,
A61K 9/16**

22 Date of filing: 25.08.89

33 Priority: 26.08.88 GB 8820327

43 Date of publication of application:
04.04.90 Bulletin 90/14

64 Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

71 Applicant: **MAY & BAKER LIMITED**

Dagenham Essex RM10 7XS(GB)

72 Inventor: **Michell, Robin Paul**
c/o May & Baker Limited
Dagenham Essex, RM10 7XS(GB)

74 Representative: **Bentham, Stephen et al**
J.A. Kemp & Co. 14 South Square Gray's Inn
London WC1R 5EU(GB)

54 **Morphine-containing composition.**

57 In an effervescent formulation containing morphine, inclusion of the morphine in the basic component gives superior storage stability.

EP 0 361 680 A2

MORPHINE-CONTAINING COMPOSITION

This invention relates to a novel pharmaceutical formulation and a process for its preparation.

Effervescent formulations are a particularly acceptable way of presenting many drugs to patients, especially if they need to be taken on a long term or regular basis.

Effervescence is the evolution of bubbles from a liquid, for example as a result of chemical action. In the case of pharmaceutical products this gas is normally carbon dioxide which is liberated by the reaction between a physiologically acceptable acid (e.g. citric, tartaric or malic acid) and a source of carbonate (such as sodium carbonate, sodium bicarbonate or a mixture thereof). It is convenient for these basic and acidic components of the "effervescent couple" to be separately granulated (e.g. by wet granulation, preferably in water), dried and then combined prior to or during packaging. The resultant mixture will then produce effervescence on being added to water.

Morphine is a drug which is often taken on a long term or regular basis and although it is available in a number of forms it has so far not been produced in an effervescent formulation.

It is known that morphine is normally degraded by oxidation, promoted by a wide variety of circumstances, and that this occurs more readily in basic media. It would therefore appear obvious to incorporate the morphine into the acid component of the effervescent couple. A further advantage would appear to be that ascorbic acid could be incorporated in this acidic mixture as an antioxidant. When such a composition is made up however, it is found that a significant decrease in activity occurs during storage. Analysis shows that this is due to esterification of phenolic groups in the morphine by the acids.

It has surprisingly been found that incorporation of the morphine in the basic component of an effervescent couple does not lead to any substantial loss in activity, even when it is in contact with granules of the acidic component.

Thus the invention provides a granule for inclusion in an effervescent formulation comprising morphine or a pharmaceutically acceptable salt thereof and the basic component of an effervescent couple.

The basic component is preferably sodium carbonate, sodium bicarbonate or a mixture thereof.

The invention also provides an effervescent formulation comprising such granules.

The morphine is generally present in the form of a pharmaceutically acceptable salt, for example morphine hydrochloride or morphine sulphate.

The stability of the effervescent morphine formulation according to the invention allows it to be readily incorporated into unit dosage forms, especially sachets. These typically contain 5, 10 or 30mg of morphine sulphate and dissolution of the contents of one or two of them in water allows a number of doses of from 5 to 60mg - or more if required - to be conveniently prepared and taken.

Granules containing the basic component of the couple are typically prepared by dry mixing morphine sulphate, sodium bicarbonate and a solid binder material such as polyvinylpyrrolidone (PVP), granulation in an aqueous solution of binder (again typically PVP in a concentration of for example 20% w/w), drying and milling. The PVP used can be for example PVP K30. Granulation may be performed in a high speed granulator (e.g. a Fielder or Diosna granulator), drying in a fluid bed drier (e.g. as manufactured by Glatt or Aeromatic) or an oven, typically at 60°C, and milling on a 2mm screen (e.g. Glatt Quicksieve).

The relative amounts of solid and aqueous binder (PVP) depend - as normal in granulation processes - on the scale of the process and can be easily determined by those skilled in the art.

Acidic granules can be prepared in a similar fashion starting from, for example, tartaric acid and/or citric acid and binder (PVP) and can also include ascorbic acid.

The final product can then be obtained by mixing these two granular materials with extragranular components such as sodium carbonate, sweeteners (e.g. aspartame) and flavourings (e.g. Lemon Juice Flav-O-Lok). This can be carried out in a blender, such as an Oblicone cone blender, a Turbula mixer or a Flow-bin type blender.

The following Examples illustrate the invention:

Example 1

Basic granules were formed by dry-mixing morphine sulphate B.P. (17.5g) sodium bicarbonate B.P. (2813g) and solid PVP, granulating with an aqueous solution of PVP (PVP K30, total weight of PVP used 63.7g), drying at 60°C and passing through a 2mm screen.

Acidic granules were prepared in a similar manner using tartaric acid B.P. (2013g), anhydrous citric acid B.P. (1224g) and solid and aqueous PVP (total weight 30.1g).

The two batches of granules were then mixed together along with sodium carbonate BPC (703.5g), aspartame ('Nutrasweet', 105g) and 'Lemon Juice Flav-O-Lok 610406E' flavouring (28g), to produce a product having the following overall composition (w/w):-

Morphine sulphate	0.25%
PVP	1.35%
Sodium bicarbonate	40.2 %
Tartaric acid	28.75%
Citric acid	17.5 %
Sodium carbonate	10.05%
Aspartame	1.5 %
Flav-O-Lok	0.4 %

This was then filled into sachets, each of which nominally contained 5mg of morphine sulphate (total sachet contents approximately 2g)

Examples 2 and 3

Sachets nominally containing 10 and 30mg of morphine sulphate in a total weight of 2g were prepared in a similar manner - the appropriate weight of sodium bicarbonate being replaced by morphine sulphate in the initial basic mix.

Reference Example

An unsatisfactory (unstable) composition was prepared in a similar manner by mixing acidic granules made from morphine sulphate (17.5g), citric acid (1224g), tartaric acid (2010g) and PVP (30.2g) and basic granules made from sodium bicarbonate (2813g) and PVP (64.3g) with sodium carbonate (703.5g), aspartame (105.5g) and Flav-o-Lok (28.1g).

The relative stability of the formulation according to the invention is shown in Table I. Samples were prepared in a similar manner to those in Example 1 and the Reference Example above.

Table I

Conditions	morphine sulphate content (mg/sachet)	
	morphine in acidic granules	morphine in basic granules
Initial	4.97	5.04
one month at:- room temperature	4.69 (94.4%)	4.93 (97.8%)
22° C/55%r.h.*		4.95 (98.2%)
37° C/80%r.h.	4.52 (90.9%)	4.87 (96.8%)
45° C/ambient humidity	4.04 (81.3%)	

* r.h. = relative humidity

Similar samples with morphine in the basic granules were also tested as shown in Table II.

Table II

test conditions	% morphine still present after		
	3 months	6 months	12 months
22 ° C/55%r.h.	98.4	97.4	95.6
37 ° C/ambient humidity	96.0	95.4	92.7
37 ° C/80%r.h.	100.0	98.2	94.6
45 ° C/ambient humidity	94.8	96.0	not tested

Samples containing 30mg morphine sulphate in the basic granules showed no significant loss in active material content under any of the conditions listed above.

Claims

1. A granule for inclusion in an effervescent formulation comprising morphine or a pharmaceutically acceptable salt thereof and the basic component of an effervescent couple.

2. A granule according to claim 1, wherein the basic component is sodium carbonate, sodium bicarbonate or a mixture thereof.

3. A granule according to claim 1 or 2, which comprises a solid binder material.

4. A granule according to claim 3, wherein the solid binder material is polyvinylpyrrolidone.

5. A granule according to any one of the preceding claims in which the morphine is present as morphine sulphate.

6. An effervescent formulation which comprises granules according to any one of claims 1 to 5.

7. An effervescent formulation according to claim 6, which further comprises acidic granules.

8. An effervescent formulation according to claim 7, in which the acid granules comprise tartaric or citric acid and a binder.

Claims for the following Contracting States: GR,ES

1. A process for producing granules for inclusion in an effervescent formulation comprising formulating morphine or a pharmaceutically acceptable salt thereof and the basic component of an effervescent couple.

2. A process according to claim 1, wherein the basic component is sodium carbonate, sodium bicarbonate or a mixture thereof.

3. A process according to claim 1 or 2, which further comprises formulating a solid binder material.

4. A process according to claim 3, wherein the solid binder material is polyvinylpyrrolidone.

5. A process according to any one of the preceding claims in which the morphine is present as morphine sulphate.

6. A process for producing an effervescent formulation which comprises formulating granules according to any one of claims 1 to 5.

7. A process according to claim 6 which further comprises formulating acidic granules.

8. A process according to claim 7 in which the acidic granules comprise tartaric or citric acid and a binder.